Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 12/4/2019 6:58:23 PM
To: Jerry Campbell [JCampbell@ramboll.com]; Harvey Clewell [HClewell@ramboll.com]
CC: Robinan Gentry [rgentry@ramboll.com]; Walsh, Patrick [patrick-walsh@denka-pe.com]; Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]; Jones, Samantha [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eac77fe3b20c4667b8c534c90c15a830-Jones, Samantha]; Lavoie, Emma [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=86ac7844f12646c095e4e9093a941623-Lavoie, Emma]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Kirby, Kevin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cbb65672f6f34545be460a66ff6fa969-Kirby, Kevin]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Morozov, Viktor [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=03cc9abb639c453fabc2bbb3e4617228-Morozov, Viktor]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; White, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4e179825823c44ebbb07a9704e1e5d16-White, Paul]; Hawkins, Belinda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=075561d171e845828ec67a945663a8e6-Hawkins, Belinda]; cvanlandingham@ramboll.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usereda39e51]
Subject: RE: Chloroprene PBPK: in vitro data / parameters

Jerry,

I thought it more credible to think that the loss is an atmospheric thing… leakage around the vial cap.

But then why does the rate equation have "P1" in it, giving the corresponding concentration in the liquid (with the implicit assumption that they are at equilibrium)? But one could just take the current value (distribution) of RLOSS and multiply by P1, then take P1 out of the equation and get the same results. So doing that won't change the metabolic estimates.

-Paul

From: Jerry Campbell <JCampbell@ramboll.com>
Sent: Wednesday, December 04, 2019 1:21 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>; cvanlandingham@ramboll.com
Subject: RE: Chloroprene PBPK: in vitro data / parameters

Paul,

It looks like L/hr/g for RLOSS is a typo. The in vitro model equation for background loss does not include protein adjustment:

(line 70 in the in vitro model)
RRLoss = RLOSS*(CA1*P1) !rate of loss from vial

Where RLOSS is the L/hr background loss, CA1 is the air concentration in the vial and P1 is the media:air partition coefficient.

RLOSS is read directly from the distribuiton and never multiplied by any adjustement factor. What we do know is that RLOSS is based on control vials that contained both 1 and 2 mg/mL protein and that there appears to be no difference in background loss due to protein level. RLOSS would most likely represent atmospheric loss from the system. The incorporation of background loss should be included in our report and we will make the changes.

Jerry Campbell

Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

Ramboll
3214 Charles B. Root Wynd
Suite 130
Raleigh, NC 27612
USA
https://ramboll.com

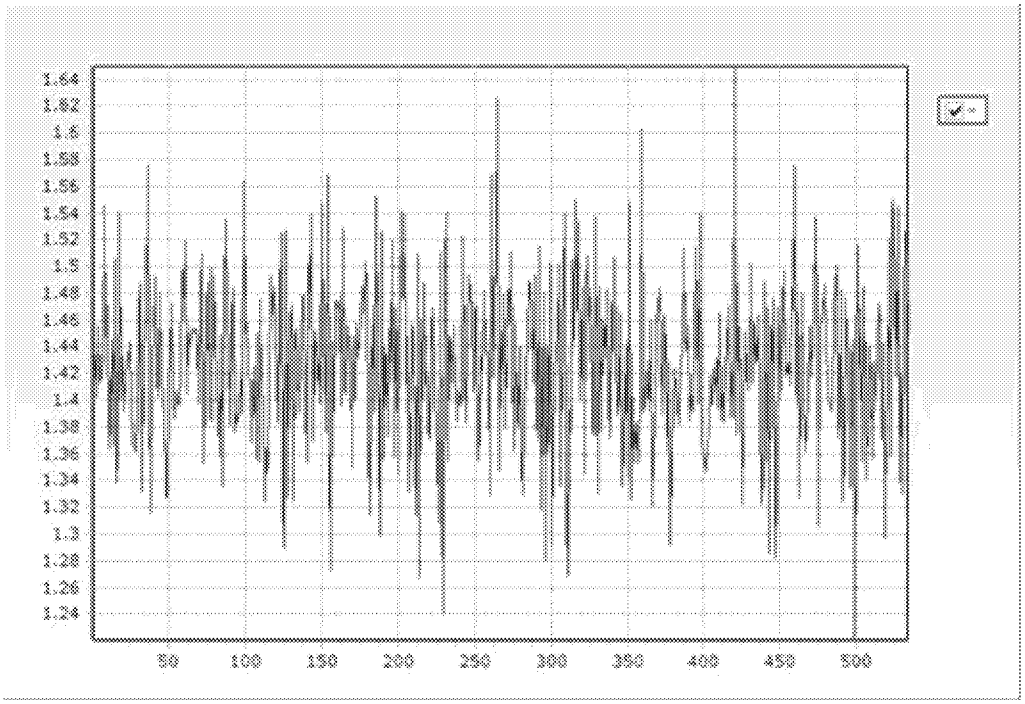
From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Wednesday, December 4, 2019 10:18 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>; Cynthia Van Landingham <cvanlandingham@ramboll.com>
Subject: RE: Chloroprene PBPK: in vitro data / parameters

Thanks…. I had done a quick scan through the report looking for tables or figures showing the results. I do see the following now:

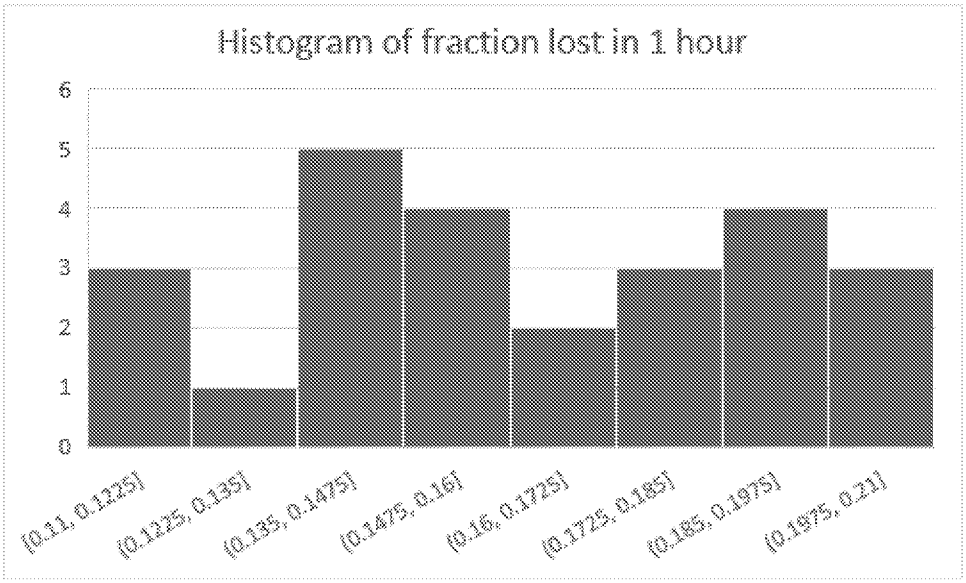
"The first-order rate constant included in the model to account for the background loss was based on the resulting posterior distribution [95th, 50th and 5th percentile of 1.5, 1.4, and 1.3 L/hr/g, respectively]" But the background loss wouldn't depend much on protein concentration, I'd think…

First: what you've provided are control data from the Yang paper, and the loss rate is based on those. What I don't have then are any control data from the Himmelstein et al. (2004) paper. But I think it will be worth comparing predictions using this control loss rate to plots from that paper, to assure they are reasonably consistent.

This is a plot of the 'ControlData' from the MCMC analysis (1000*exp(ControlData), since it's log-transformed and to convert units), so apparently a sample from the posterior chain, sampling from a uniform distribution. Presumably that's for the mean control rate. (Scroll down for more.)



On the other hand, I took the fraction lost from each control experiment in the spreadsheet and treated it as a measurement of loss (didn't convert to a rate constant), to see what the distribution of loss rate between experiments looks like. Histogram below. I think this represents the variation from vial to vial, cap to cap, etc., and it looks more like a normal distribution over ~ 2x (max/min), or +/- 50% of the mean. My assumption is that the loss rate (fraction or rate constant) is independent of the gas concentration, tissue, species, sex, but each time a person puts a cap on a vial, the seal could vary in quality. The fact that the loss rate in a given vial can be measured accurately (when there's no metabolism) doesn't reduce the uncertainty in the exact rate in an active vial. The data below indicates the range of that uncertainty to me. I don't see any particular pattern among the individual data sets, so no reason not to look at them as one group. (Keep scrolling down.)



Conversely, I think the 95% CI on the assumed distribution for background loss is only about 16%, +/- 8% of the mean. If the assumed background loss is treated as having a distribution this tight, that will result in under-estimation of the uncertainty in the metabolic parameters (i.e., the CI on the population mean value)… most significantly for the tissues where metabolism is low.

This doesn't impact a conclusion as to whether the resulting mean parameters adequately represent the data as such, but whether the confidence intervals in the report are valid measures of uncertainty in those values. This control information will be part of what I think we'll want a statistician peer reviewers to consider. **The report should also describe how the control loss rate (distribution) was estimated, presumably the same statistical model used, and how it was sampled during the estimation of metabolic parameters.**

I still have to QA the two human scripts (liver and lung). So far I've found only a couple of very small differences in numbers (e.g., 0.108 in the appendix table vs. 0.11 in the script), with negligible impact on the fits. I may also want to overlay some of the data (from scripts) on copies of figures from Himmelstein, to assure they match. I don't need to QA all data, just spot-check. But I'm mostly through.

-Paul

From: Harvey Clewell <HClewell@ramboll.com>
Sent: Tuesday, December 03, 2019 4:47 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>; cvanlandingham@ramboll.com
Subject: RE: Chloroprene PBPK: in vitro data / parameters

HI Paul

We used the chain that we sent you, which represents the posterior distribution for the loss rate in the controls from the 2009 report (IISRP-17520-1388).

With kind regards
Harvey Clewell
PhD, DABT, FATS
Principal Consultant
Ramboll Environment and Health Consulting
Raleigh, NC 27612 USA
hclewell@ramboll.com
919-452-4279

From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Tuesday, December 3, 2019 1:41 PM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>; Cynthia Van Landingham <cvanlandingham@ramboll.com>
Subject: RE: Chloroprene PBPK: in vitro data / parameters

Harvey, all,

This is fairly small but niggling thing: when the 2nd set of experiments were run, the incubation vials were slightly different (smaller volume) and the sampling volume, maybe the syringes, used were different. In the model files difference in vial volume, < 0.3 mL, is tracked. But the system loss rate, which might depend on small things (e.g., quality of seal formed by the vial cap) is assumed to be unchanged. Do you recall if any control incubations were done in 2009, that could be used to check that? I don't see any data in the Yang paper or Matt's report.

For the female mouse lung the loss is about 15% of the metabolic conversion, so it's not a huge factor. But as I go through the QA and see the VVIAL set to slightly different values for the two sets of experiments (and this makes a small but noticeable difference in the plots), it stands out that RLOSS, which is set to 4 significant figures, is assumed to be exactly the same.

-Paul

From: Cynthia Van Landingham <cvanlandingham@ramboll.com>
Sent: Monday, November 18, 2019 2:00 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>
Subject: RE: Chloroprene PBPK: metabolic parameters / IVIVE calculations

Paul,
Attached is the paper that you requested in your e-mail below. I will get back to you as soon as I can with the answers to your other questions.

Cynthia

Cynthia Van Landingham
Senior Managing Consultant

D +1 (318) 3982091
M +1 (318) 6147920
cvanlandingham@ramboll.com

From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Monday, November 18, 2019 1:38 PM
To: Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>
Cc: Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>
Subject: Chloroprene PBPK: metabolic parameters / IVIVE calculations

Greetings,

While I can't speak to the ultimate numerical significance, there are a number of discrepancies in and among the descriptions and calculations for IVIVE of metabolic parameters (i.e., between statements in the main report, p. 9, Supp Mat C, and the spreadsheet, Supp Mat D), and a couple of choices that I'm questioning. See below.

I would need to request a copy of Houston and Galetin (2008), which might take a few days, so it would help if Ramboll can send a copy.

I've highlighted the items that seem most significant, where corrections in the IVIVE spreadsheet appear to be needed or the justification (40 vs. 45 mg/g microsomal protein in rat liver) seems a bit weak. A copy of the spreadsheet where I've highlighted cells of concern is attached.

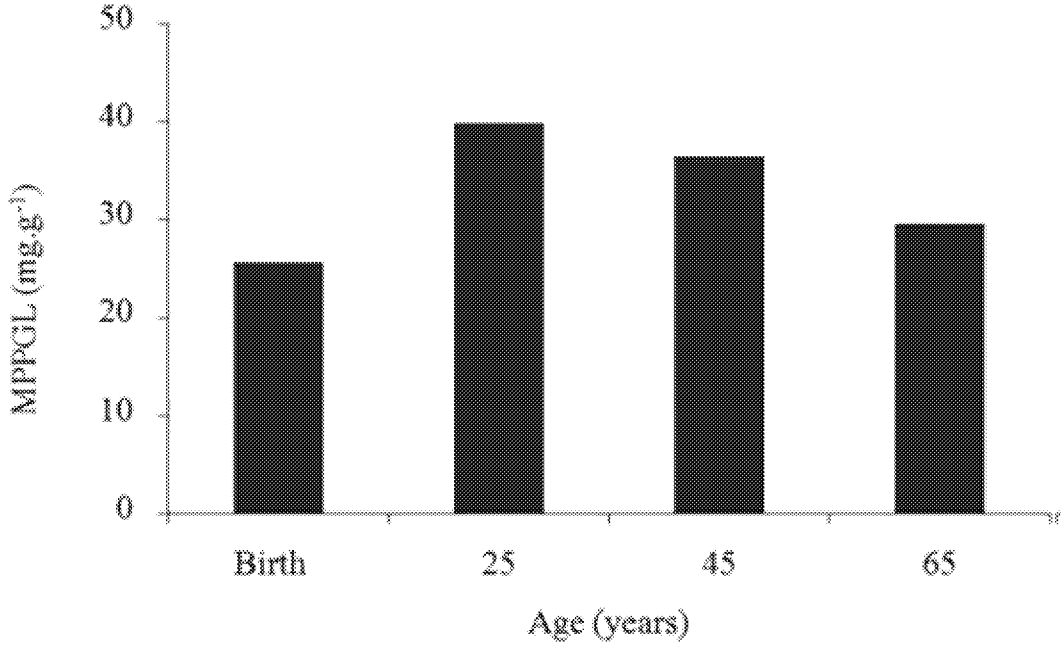
-Paul

Metabolic parameters and IVIVE extrapolation
The following are found in the spreadsheet, EPA Supp Mat D, in the "IVIVE" tab.

- **BW values for mice and rats, cells C22-C25**: these differ from the standard BW values listed in table S-1. For the sake of consistency, and since the tissues used to obtain microsomes were likely from juvenile/young adult

animals, it might be better to use the lower, standard BW values from Table S-1. Alternately the Supp Mat C, Table 1 (which match the values in the Supp Mat D, IVIVE table), should be used in the model code for dose calculations in the absence of study-specific values.

- **Liver and lung microsome content, cells G22-G27 (liver) and cells H22-H26 (lung in all species)**:
  - **Mouse liver:** From Supp Mat C, value of 35 mg/g is from Medinsky et al. (1994), so reference in cell G27 is incorrect (says "rat value used for mouse")
  - **Rat liver:**
    - report p. 9 says 45 mg/g used for rats, not consistent with 40 in IVIVE spreadsheet (cells G24-25);
    - need to obtain Houston and Galetin (2008);
    - Supp Mat C says an average of values for rat from Medinsky et al. (1994) (sentence is confusing, "For mouse, 35 mg/g liver was reported by Medinsky et al. (1994) for both rat and mouse,") and 45 mg/g from Houston and Galetin, but it's not entirely clear why a cross-species average would be used for the rat, but not the mouse ; if Medinsky et al. (1994) also measured 35 mg/g from rat liver, then an average may make sense...
    - In Barter et al. (2007), Figure 2, part A, there appear to be many papers reporting 45 mg/g for the rat, so the value of 45 mg/g may be better supported;
    - reference in cell 27 just cites Houston and Galetin (2008), not consistent with "40".
  - **Human liver:**
    - Text in main report, p. 9, says 40 mg/g, which matches the value listed in Supp Mat C;
    - *But* IVIVE cell G26 has **50** mg/g;
    - Supp Mat C, "Based on their meta-analysis and consensus report of the human data (Barter et al., 2007), 40 mg/g liver is recommended for human adults for chloroprene IVIVE-PBPK modeling," so it would be less confusing if the main report and IVIVE cell G27 cited this reference, not Barter et al. (2008)
    - From Barter et al. (2007): "Values of MPPGL were approximately 36 and 31% lower in newborn and elderly (80 years) individuals than those in a 25-year-old individual (typically the age of individuals used in clinical pharmacology studies). The use of a value of MPPGL of 40 mg g^{-1}, determined for a young adult, would be expected to result in an overprediction of clearance in very young or very old patients. Therefore, MPPGL values relevant to the age of the population in which predictions are being made should be used in IVIVE." Image below is from Barter et al. (2008). Should risk assessment be focused on young adults, or entire population; i.e., use more of a population-average value from this reference? The young-adult value of 40 mg/g likely will be most health-protective.
    - But the statement in Supp Mat C appears to mis-represent the conclusions of Barter et al. (2007): it should be made clear that this value is the recommendation of the model authors, not the cited paper.



- **Lung:** value of 23 mg/g in cells H22-26 does match Himmelstein et al. (2004b), but text in the report says 20 mg/g, and this is the conclusion after some discussion in Supp Mat C. Hence it appears that the value in the IVIVE tab (used) should be 20 mg/g and the reference in cell H27 should be changed to Medinsky et al. (1994).

- **In Vitro Values of KFLUC for female rat (cell V33) and male rat (cell V38)**: These cells have calculations which are not explained and do not take values from the in vitro metabolic results; e.g., "=1.2/(0.82*2)/1000" in cell V33, which should be just equal to Parameter_Summary cell I18.